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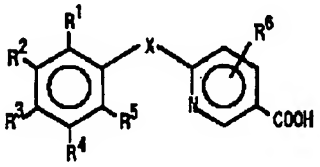
(54)【発明の名称】　皮膚外用剤

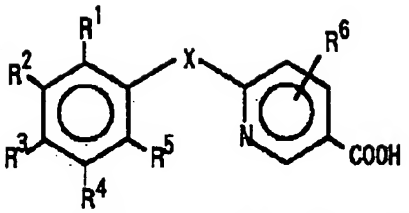
(57)【要約】

【構成】　下記の式（式中、$R^1$，$R^2$，$R^3$，$R^4$，及び$R^5$はそれぞれ独立に水素、$C_{1-6}$アルキル基等を示し、Ｘは-NH-CO-又は-CO-NH-を示し、$R^6$は水素、$C_{1-6}$アルキル基等を示す）で示される化合物を含む皮膚外用剤。

【化１】




【効果】　優れた皮膚劣化防止作用を有し安定で経皮吸収が少なく安全性が高い。また容易に代謝されるのでレチノイド作用による副作用が少ない。



（式中、$R^1$，$R^2$，$R^3$，$R^4$，及び$R^5$はそれぞれ独立に水素、$C_{1-6}$アルキル基、水酸基、ハロゲン原子又は$C_{1-6}$アルコキシ基を示し、X は-NH-CO- 又は-CO-NH- を示し、$R^6$は水素、$C_{1-6}$アルキル基、水酸基、ハロゲン原子、又は$C_{1-6}$アルコシキ基を示す）で示される化合物を含む皮膚外用剤を提供するものである。

【０００９】上記本発明の好ましい態様によれば、皮膚劣化防止作用を有する上記皮膚外用剤；上記化合物が実質的に経皮吸収されない化合物である上記の皮膚外用剤；及び、局所的及び／又は全身的細胞障害性が軽減された上記の皮膚外用剤が提供される。また、本発明の別の態様によれば、上記の化合物を有効成分として含む外用の皮膚劣化防止剤が提供される。

【００１０】本発明の皮膚外用剤に含まれる上記化合物において、$R^1$，$R^2$，$R^3$，$R^4$，及び$R^5$は、それぞれ独立に、水素、$C_{1-6}$アルキル基、水酸基、ハロゲン原子又は$C_{1-6}$アルコキシ基を示す。$C_{1-6}$アルキル基としては、直鎖または分枝アルキル基のいずれを用いてもよく、より具体的には、メチル基、エチル基、n-プロピル基、イソプロピル基、n-ブチル基、sec-ブチル基、tert- ブチル基、n-ペンチル基、イソペンチル基、ネオペンチル基、又はn-ヘキシル基などを用いることができる。これらのうち好ましくは、エチル基、イソプロピル基、またはtert- ブチル基を用いることができる。$C_{1-6}$アルコキシ基としては、直鎖または分枝アルコキシ基のいずれを用いてもよく、より具体的には、メトキシ基、エトキシ基、n-プロポキシ基、イソプロポキシ基、n-ブトキシ基、sec-ブトキシ基、tert- ブトキシ基などを用いることができる。ハロゲン原子としては、フッ素原子、塩素原子、臭素原子、またはヨウ素原子のいずれを用いてもよい。

【００１１】このような化合物のうち、例えば、上記$R^1$，$R^2$，$R^3$，$R^4$，及び$R^5$から選ばれる隣接又は非隣接の２つの置換基が同一又は異なるアルキル基である化合物は、本発明の外用剤の成分として好ましい化合物である。例えば、$R^2$と$R^3$，または$R^2$と$R^4$がともにアルキル基である化合物が好ましい。このような化合物のうち、アルキル基がエチル基、イソプロピル基、または tert-ブチル基である化合物がより好ましく、$R^2$及び$R^3$がともにエチル基である化合物、$R^2$及び$R^4$がともにtert- ブチル基である化合物が特に好ましい。

【００１２】$R^6$は水素原子、$C_{1-6}$アルキル基、水酸基、ハロゲン原子、又は$C_{1-6}$アルコシキ基を示す。$C_{1-6}$アルキル基、ハロゲン原子、又は$C_{1-6}$アルコシキ基としては上記のものを用いることができる。$R^6$は、ピリジン環の2-位，5-位，又は6-位の任意の位置に置換することができる。これらのうち、$R^3$が水素原子である化合物が好ましい。

【００１３】より具体的にいうと、本発明の皮膚外用剤の成分としては、6-(3,4- ジエチルフェニルカルバモイル）ニコチン酸；6-(3,4- ジエチルフェニルカルボキサミド）ニコチン酸；6-(3,5- ジ -t-ブチルフェニルカルバモイル）ニコチン酸；又は6-(3,5- ジ -t-ブチルフェニルカルボキサミド）ニコチン酸などの化合物が好ましいが、本発明の皮膚外用剤の成分は、これらの好ましい化合物に限定されることはない。なお、本発明の皮膚外用剤には、上記の化合物の１種あるいは２種以上を組み合わせて用いることが可能である。また、上記の化合物の任意の塩基付加塩や任意の水和物を用いてもよい。塩基付加塩としては、例えば、ナトリウム塩、カリウム塩、カルシウム塩、マグネシウム塩などの金属塩や、アンモニウム塩、有機アミン塩などを用いることができる。

【００１４】本発明の皮膚外用剤における上記化合物の配合量は特に限定されず、化合物の種類や適用目的、皮膚の状態などにより適宜増減することができるが、一般的には、皮膚外用剤全量中 0.005～5.0 重量%、好ましくは 0.05 ～1.0 重量%である。なお、一般的には、上記化合物の配合量が0.005 重量%未満では効果は十分でない場合があり、また、5.0 重量%を越えて配合しても皮膚劣化防止効果の増強は見られない場合があるので、配合量が極端に上記の範囲を逸脱することは好ましくない。

【００１５】上記化合物の一部は公知の化合物であり、例えば、特開平6-263702号公報及び欧州特許公開第 617 020-A1に記載された方法により容易に製造可能である。また、新規化合物については、本明細書の実施例に記載された方法や上記の刊行物に記載された方法に従って、あるいはそれらに加えて、さらに特開平7-17854 号公報及びPCT 国際公開WO 93/6086号などの刊行物に記載された方法を参照することにより、当業者に容易に製造可能である。

【００１６】本発明の皮膚外用剤には、上記の化合物の他、通常の化粧品や医薬品、医薬部外品等の皮膚外用剤に用いられる他の成分、例えば、リボフラビン、酪酸リボフラビン、フラビンアデニンジヌクレチド等のビタミン$B_2$類；ピリドキシン塩酸塩、ピリドキシンジオクタノエート等のビタミン$B_6$類；L-アスコルビン酸、L-アスコルビン酸ジパルミチン酸エステル、L-アスコルビン酸-2- 硫酸ナトリウム等のビタミンC 類；パントテン酸カルシウム、D-パントテニルアルコール、パントテニルエチルエーテル、アセチルパントテニルエチルエーテル等のパントテン酸類；エルゴカルシフェロール、コレカルシフェロール等のビタミンD 類；ニコチン酸、ニコチン酸アミド、ニコチン酸ベンジル等のニコチン酸類；

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【００１７】α－トコフェロール、酢酸トコフェロール、ニコチン酸 DL-α－トコフェロール、コハク酸 DL-α－トコフェロール等ノビタミンE 類；ビタミンP 、ビオチン等のビタミン類；グリシン、アラニン、バリン、ロイシン、イソロイシン、セリン、スレオニン、アスパラギン酸及びその塩、グルタミン酸及びその塩、リジン、アルギニン、システイン、シスチン、メチオニン、フェニルアラニン、チロシン、ヒスチジン、トリプトファン、プロリン、N-パルミトイル L- アスパラギン酸ジエチル、N-ヤシ油脂肪酸 -L-グルタミン酸ナトリウム等のN-アシル酸性アミノ酸塩、ヤシ油脂肪酸サルコシントリエタノールアミン、ラウロイルメチル－β－アラニンナトリウム等のアシル中性アミノ酸塩、ピロリドンカルボン酸及びその塩、POE(40) 硬化ヒマシ油モノピログルタミン酸モノイソステアリン酸ジエステル、N-ヤシ油脂肪酸 -L-アルギニンエチルエステル-DL-ピロリドンカルボン酸塩等のアミノ酸及びアミノ酸誘導体；

【００１８】アボガド油、パーム油、ピーナッツ油、牛脂、コメヌカ油、ホホバ油、月見草油、カルナバロウ、ラノリン、流動パラフィン、スクワラン、パルミチン酸イソステアリル、イソステアリルアルコール、トリ -2-エチルヘキサン酸グリセリン等の油分；グリセリン、ソルビトール、ポリエチレングリコール、1,3-ブチレングリコール、コラーゲン、ヒアルロン酸、コンドロイチン硫酸、デキストラン硫酸ナトリウム等の保湿剤；エリソルビン酸ナトリウム、パラヒドロキシアニソール等の酸化防止剤；ステアリル硫酸ナトリウム、セチル硫酸ジエタノールアミン、セチルトリメチルアンモニウムサッカリン、イソステアリン酸ポリエチレングリコール、アラキン酸グリセリル、ジグリセリンジイソステアレート、リン脂質等の界面活性剤；エチルパラベン、ブチルパラベン等の防腐剤；

【００１９】グリチルリチン酸誘導体、グリチルレチン酸誘導体、サリチル酸誘導体、ヒノキチオール、酸化亜鉛、アラントイン等の消炎剤；胎盤抽出物、グルタチオン、ユキノシタ抽出物等の美白剤；オウバク、オウレン、シコン、シャクヤク、センブリ、バーチ、セージ、ビワ、ニンジン、アロエ、ゼニアオイ、アイリス、ブドウ、ヨクイニン、ヘチマ、ユリ、サフラン、センキュウ、ショウキョウ、オトギリソウ、オノニス、ローズマリー、ニンニク等の抽出物；ローヤルゼリー、感光素、コレステロール誘導体、幼牛血抽出物等の賦活剤；γ－オリザノール等の血行促進剤；硫黄、チアントール等の抗脂漏剤；カルボキシビニルポリマー、カルボキシメチルセルロース、カルボキシヒドロキシプロピルセルロース等の増粘剤；香料；水；アルコール；チタンイエロー、カーサミン、ベニバナ赤等の色剤；又は、ポリエチレン、ナイロン等の樹脂粉末等を必要に応じて適宜配合することができる。

【００２０】本発明の皮膚外用剤には、皮膚疾患の予防

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や治療に有用な医薬の有効成分及び／又は光障害の防止に有用な紫外線吸収剤等を配合してもよい。このような医薬の有効成分としては、例えば、ステロイド系化合物や抗生物質などを挙げることができる。紫外線吸収剤としては、例えば、パラメトキシケイ皮酸 -2-エトキシエチル、パラメトキシケイ皮酸イソプロピル、ジイソプロピルケイ皮酸エステル、パラメトキシケイ皮酸エチルヘキシル、ジパラメトキシケイ皮酸モノ -2-エチルヘキサン酸グリセリル、メトキシケイ皮酸オクチル等のケイ皮酸紫外線吸収剤；ブチルメトキシベンゾイルメタン、4-tert- ブチル-4´－メトキシ -ジベンゾイルメタン等のベンゾイルメタン系紫外線吸収剤；グリセリルーモノ -2-エチルヘキサノイルージーパラメトキシベンゾフェノン、 2,2´- ジヒドロキシ -4-メトキシベンゾフェノン、 2,2´- ジヒドロキシ-4,4´- ジメトキシベンゾフェノン、2-ヒドロキシ -4-メトキシベンゾフェノン、2-ヒドロキシ -4-メトキシベンゾフェノン -5-スルホン酸ナトリウム等のベンゾフェノン系紫外線吸収剤；

【００２１】オルトアミノ安息香酸メチル、パラジメチルアミノ安息香酸 -2-エチルヘキシル、パラジメチルアミノ安息香酸オクチル等の安息香酸系紫外線吸収剤；グリセリルパラアミノベンゾエート、アミルーパラージメチルアミノベンゾエート、エチル -4- ビスヒドロキシプロピルアミノベンゾエート等のベンゾエート系紫外線吸収剤；2-エチルヘキシル -2-シアノ-3,3´- ジフェニルアクリレート、ジガロイルトリオレエート、サリチル酸 -2-エチルヘキシル、サリチル酸ホモメチル、グアイアズレン、ウロカニン酸等のその他の紫外線吸収剤などを用いることができる。

【００２２】本発明の皮膚外用剤は、日光照射による光障害、加齢に伴う皮膚のしわ、たるみ、つやの消失等の皮膚劣化を防止する作用を有している。従って、本発明の皮膚外用剤を日常的な皮膚の手入れや日光照射後に適用することにより、皮膚の劣化を防止することができ、若々しい健康な皮膚の状態を維持することが可能である。なお、本発明の皮膚外用剤の剤形は特に限定されず、例えば化粧水等の可溶化系、乳液、クリーム等の乳化系、あるいは軟膏、分散剤、エアゾール状等の剤形をとることができる。使用方法は特に限定されないが、例えば、クリーム剤などの剤形の場合には、適量を指でとって顔や手に薄く満遍なく塗布し、好ましくはマッサージなどによって皮膚に擦り込めばよい。以下、本発明を実施例によりさらに具体的に説明するが、本発明はこれらの実施例に限定されることはない。

【００２３】

【実施例】

(1) 化合物の製造

例１： 6-(3,4- ジエチルフェニルカルバモイル) ニコチン酸

濃硫酸 8.1 ml 及び硝酸 (d=1.42) 5.16 ml の混合液を

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1,2- ジエチルベンゼン 9.96 g (74.3 mmol) 中に0℃で滴下し、同温度で2時間反応させた。反応液を氷中に注入し、エーテルで抽出した。有機層を水で3回、飽和重曹水、飽和食塩水の順に洗浄し、脱水後に溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーにより精製し（富士シリシア, BW-820MH, 500 g ；展開溶媒 n- ヘキサン／塩化メチレン=19/1)、3,4-ジエチルニトロベンゼン 7.8 gを得た（収率：58.6%)。上記3,4-ジエチルニトロベンゼン 6 g (36 mmol)及び 5% Pd/c 0.6 g をエタノール 100 ml 中に加え、常温、常圧で接触還元した。触媒を濾去した後、溶媒を留去して3,4-ジエチルアミノベンゼン 4.89 g を得た（収率：91.2%)。

【００２４】無水ベンゼン 500 ml 及びチオニルクロライド 77 ml中に3-メトキシカルボニルピリジン-2- カルボン酸 4.62 g (25 mmol) を加え、還流下で6時間反応させた。溶媒を留去し、残渣に無水ベンゼン 100 ml を加えてチオニルクロライドを共沸濃縮（3回）した。残渣に無水ベンゼン 385 ml を加えて溶解し、この溶液に 3,4- ジエチルアミノベンゼン 4.5 g (25 mmol)を乾燥ピリジン 19.2 ml及び無水ベンゼン 385 ml に溶解して室温で滴下混合し、アルゴン気流下で3時間反応させた。反応液を氷水 1925 ml中に加え、2 N HCl 77 ml を加えてよく撹拌し、酢酸エチル1.2 リットルで3回抽出した。有機層を飽和食塩水 1.2リットルで洗浄した後、硫酸マグネシウムで乾燥して濃縮乾固した。残渣をシリカゲルカラムクロマトグラフィーにより精製し（富士シリシア, BW-820MH, 500 g ；展開溶媒　酢酸エチル／n-ヘキサン= 1/3)、粗生成物 7.57 g を得た。得られた生成物をn-ヘキサン／酢酸エチルから再結晶して、6-(3,4- ジエチルフェニルカルバモイル) ニコチン酸メチル 6.35 g を得た（収率：81.4%)。

【００２５】6-(3,4- ジエチルフェニカルバモイル) ニコチン酸メチル 6 g (19.2 mmol)をメタノール 1リットルに溶解し、2 N NaOH 200 ml を加えて室温で12時間反応させた。反応液を 0.5 N HCl 1.2リットル中に加え、酢酸エチル 1.2リットルで3回抽出した。有機層を飽和食塩水 1.2リットルで洗浄した後、硫酸マグネシウムで乾燥し、溶媒留去した。残渣を酢酸エチル／エタノールから再結晶して6-(3,4- ジエチルフェニルカルバモイル) ニコチン酸 2.9 gを得た（収率：50.7%)。

淡黄色針状晶, mp 174-176℃

$^1$H NMR (400 MHz, DMSO-$d_6$, 30℃) $\delta$ : 10.57(s,1H), 9.16(d,1H,J=2Hz), 8.50(dd,1H,J=2Hz,8Hz), 8.25(d,J=8Hz), 7.71(d,1H,J=2Hz), 7.67(dd,1H,J=2Hz, 8Hz), 7.14(d,J=8Hz), 2.61(m,4H), 1.19(t,3H,J=7.5Hz), 1.16(t,3H,J=7.5Hz)

元素分析 ($C_{17}H_{18}N_2O_3$): 理論値 C 68.44 ; H 6.08 ; N 9.39 ；実測値 C 68.70 ; H 6.11 ; N 9.41

【００２６】例２： 6-(3,4-ジエチルフェニルカルボキサミド) ニコチン酸

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塩化アルミニウム ($AlCl_3$) 11.4 g (62.2 mmol) のニトロメタン溶液 (60 ml)に、塩化アセチル 6.44 g (82.0 mmol) 及び 1,2- ジエチルベンゼン 9.50 g (70.8 mmol) のニトロメタン溶液 (60 ml)を0℃で1時間かけて滴下混合した。反応液を室温で2時間撹拌し、氷水 150 ml に注入した。この混合物に酢酸エチル150 ml を加え、セライトで濾過し、水層を酢酸エチル (100 ml) で抽出した。酢酸エチル層を集めて、水、飽和重曹水、水、飽和食塩水 (各 100 ml)で順次洗浄した後、硫酸ナトリウムで乾燥して溶媒を留去した。残査を真空蒸留(bp 95℃/1.2 mmHg)して3,4-ジエチルアセトフェノン 12.0 g を得た（収率：96%)。

【００２７】3,4-ジエチルアセトフェノン 11.0 g (62 mmol) のジオキサン (160 ml) 溶液に 5 % NaOCl水溶液 (275 ml) 及び 25 % NaOH水溶液 (33 ml)の混液を滴下混合し、50～60℃で2時間反応させた。反応液を冷却して氷水 1リットルに注入し、$NaHSO_3$を加えた後、濃塩酸で pH 3 に調整した。この混合物を酢酸エチル(750 ml, 500 ml)で抽出した。酢酸エチル層を水、飽和食塩水 (各 500 ml)で洗浄し、硫酸ナトリウムで乾燥して溶媒を留去した。得られた粗生成物 11.0 g をn-ヘキサン 120 ml から再結晶して3,4-ジエチル安息香酸 10.2 g を得た（収率：92%)。

【００２８】3,4-ジエチル安息香酸 6.5 g(36.5 ml)の無水ベンゼン(200 ml)溶液にチオニルクロライド 28 ml を加え、還流下5時間反応させた。反応液を濃縮後、無水ベンゼン 50 mlで2回置換して濃縮した。残渣に乾燥 THF 25 mlを加えて溶解し、この溶液を 6- アミノニコチン酸メチルエステル 5.55 g(36.5 ml)及びトリエチルアミン 4.61 g(4.56 mmol)の乾燥 THF溶液(300 ml)に室温で滴下混合した。反応液を室温で3時間撹拌した。反応液を濃縮し、酢酸エチル(150 ml)および水(100 ml)を加えた。水層を酢酸エチルで抽出し(50 ml×2)、酢酸エチル層を水、飽和食塩水 (各 100 ml)で洗浄し、硫酸ナトリウムで乾燥して溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーで精製し (BW-820MH, 300 g ；展開溶媒　塩化メチレン／酢酸エチル=15/1)、9.0 g の6-(3,4- ジエチルフェニルカルボキサミド) ニコチン酸メチルおよびジアミド体の混合物を得た。

【００２９】この混合物をメタノール(650 ml)に溶解し、濃塩酸(20 ml) を加えて55℃で 2.5時間反応させた。反応液を濃縮し、飽和重曹水(400 ml)および塩化メチレン(200 ml)を加え、水層を塩化メチレンで抽出した(150 ml, 100 ml)。塩化メチレン層を水で洗浄し、硫酸ナトリウムで乾燥して溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーで精製し (BW-820MH, 250 g ；展開溶媒　ベンゼン／アセトン=30/1)し、5.5 g の粗生成物を得た。この生成物をn-ヘキサン(100 ml)から再結晶して、6-(3,4- ジエチルフェニルカルボキサミド) ニコチン酸メチル4.7 gを得た（収率：41%)。

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【００３０】6-(3,4- ジエチルフェニルカルボキサミド) ニコチン酸メチル 4.7 g(15 mmol) をメタノール(900 ml)に溶解し、2 N NaOH 170 ml を加えて室温で12時間反応させた。反応液を 0.5 N HCl(1270 ml) 中に加え、酢酸エチルで抽出した (6 リットル, 2 リットル)。有機層を飽和食塩水 (2 リットル) で洗浄した後、硫酸ナトリウムで乾燥して溶媒留去した。残渣をクロロホルム／エタノール=1/1 (720 ml) から再結晶して、6-(3,4- ジエチルフェニルカルボキサミド) ニコチン酸2.4 gを得た (収率：54%)。

無色針状晶, mp 294-295℃

$^1$H NMR (400 MHz, DMSO-$d_6$, 30℃) $\delta$ : 11.02(s,1H), 8.88(m,1H), 8.32(br d,1H,J=8Hz), 8.30(dd,1H,J=2Hz, 8.8Hz), 7.88(d,1H,J=2Hz), 7.82(dd,1H,J=2Hz,8Hz), 7.30(d,1H,J=8Hz), 2.69(q,4H,J=7.5Hz), 1.23(t,3H,J=7.5Hz), 1.19(t,3H,J=7.5 Hz)z

元素分析 ($C_{17}H_{18}N_2O_3$): 理論値 C 68.44 ; H 6.08 ; N 9.39 ；実測値 C 68.25 ; H 6.08 ; N 9.10

【００３１】例３： 6-(3,5-ジ-tert-ブチルフェニルカルボキサミド) ニコチン酸

3,5-ジ-tert-ブチル安息香酸(1,800 mg)、チオニルクロライド(3 ml)、及び無水ベンゼン (20 ml)の混合物を６時間還流した。溶媒及び過剰のチオニルクロライドを減圧留去した。残渣を無水ベンゼン (15 ml)に溶解し、6-アミノニコチン酸メチル(500 mg)、トリエチルアミン(3 ml)、無水ベンゼン (10 ml)の混合物を加えて室温で一晩反応させた。反応液を水にあけ、酢酸エチルで抽出した。有機層を水で洗浄し、硫酸ナトリウムで乾燥し、溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーで精製して 6-(3,5-ジ-tert-ブチルフェニルカルボキサミド) ニコチン酸メチルおよびジアシル体の混合物(770 mg)を得た。この混合物をメタノール (30 ml)に溶解し、濃塩酸 (1 ml) を加えて３時間還流した。溶媒を留去し、残渣に塩化メチレン及び１N重曹水を加えた。有機層を水で洗浄し、硫酸ナトリウムで乾燥して溶媒を留去した。残渣をシリカゲルカラムクロマトグラフィーで精製して 6-(3,5-ジ-tert-ブチルフェニルカルボキサミド) ニコチン酸メチルを得た。

【００３２】6-(3,5-ジ-tert-ブチルフェニルカルボキサミド) ニコチン酸メチル(93 mg)をメタノール (10 ml)に加熱溶解した。2 N NaOH (2 ml) を加え、反応液を室温下で一晩撹拌した。反応液に 2 N HClを加えて酸性にした後、溶媒を留去した。残渣に酢酸エチル及び水を加え、有機層を分離して飽和食塩水で洗浄し、硫酸ナトリウムで乾燥して溶媒を留去した。残渣をメタノール／酢酸エチルから再結晶して、6-(3,5- ジ-tert-ブチルフェニルカルボキサミド) ニコチン酸を得た。

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無色プリズム晶, mp＞ 300℃

$^1$H NMR (400 MHz, DMSO-$d_6$, 30℃) $\delta$ : 11.27(s,1H), 8.89(d,1H,J=2.2Hz), 8.34(d,1H,J=8.4Hz), 8.31(dd,1H,J=2Hz, 8.5 Hz), 7.87(d,1H,J=1.5Hz), 7.63(brt,1H), 1.34(s,18H)

元素分析 ($C_{21}H_{26}N_2O_3$): 理論値 C 71.16 ; H 7.39 ; N 7.90 ；実測値 C 71.19 ; H 7.66 ; N 7.88

【００３３】例４： 6-(3,5-ジ-tert-ブチルフェニルカルバモイル) ニコチン酸

5-メトキシカルボニルピリジン-2- カルボン酸(14 g)をベンゼン(120 ml)に溶解し、チオニルクロライド(85 ml) を加えて４時間還流した。溶媒を留去し、残渣に無水ベンゼンを加えてチオニルクロライドを留去して酸クロリドを得た。上記の酸クロリドのベンゼン溶液 (170 ml) を3,5-ジ-tert-ブチルアニリン(14.9g)のピリジン(62 ml)-ベンゼン(100 ml)溶液に20℃で滴下し、３時間反応を行った。反応液を氷水(120 ml)にあけ、1N HCl (57 ml)を加えて酢酸エチル(60 ml)で２回抽出した。有機層を0.5 N HCl (150 ml)、飽和食塩水 (150 ml×2回) で順次洗浄し、無水硫酸マグネシウムで脱水した。活性炭(850 mg)で処理して溶媒を留去し 26.8 g の残渣を得た。n-ヘキサンと酢酸エチルの混合溶媒から再結晶して 22.5 g のエステル体を得た。

【００３４】上記のエステル体をメタノール (280 ml) に懸濁して20℃以下で 2 N NaOH (125 ml)を添加し、室温で６時間反応させた。20℃以下で 1.5 N HCl (150 ml) を加え、析出した結晶を酢酸エチル 1.5リットルで抽出した。洗浄後、酢酸エチルを留去し、残渣を酢酸エチル－エタノールから再結晶して、6-(3,5-ジ-tert-ブチルフェニルカルバモイル) ニコチン酸 14.7 g を得た。

m.p. 288-289.5℃

【００３５】

(2) 皮膚外用剤の製造例

例１：化粧水

| | |
|---|---|
| 6-(3,4- ジエチルフェニルカルバモイル) ニコチン酸 | 0.05 |
| 2-ヒドロキシ -4-メトキシベンゾフェノン -5-スルホン酸ナトリウム | 0.1 |
| 酢酸トコフェノール | 0.01 |
| グリセリン | 4.0 |
| 1,3-ブチレングリコール | 4.0 |
| エタノール | 8.0 |
| ポリオキシエチレン(60)硬化ヒマシ油 | 0.5 |

| | |
|---|---|
| メチルパラペン | 0.2 |
| クエン酸 | 0.05 |
| クエン酸ソーダ | 0.1 |
| 香料 | 0.05 |
| 精製水 | 残余 |

【００３６】精製水に2-ヒドロキシ -4-メトキシベンゾフェノン -5-スルホン酸ナトリウム、クエン酸、クエン酸ソーダ、グリセリン、1,3-ブチレングリコールを溶解する。別に6-(3,4- ジエチルフェニルカルバモイル) ニコチン酸、エタノールにポリオキシエチレン(60)硬化ヒ＊マシ油、酢酸トコフェノール、香料、メチルパラペンを溶解し、この溶液を上記の水溶液に加えて、濾過して化粧水を得た。

【００３７】

例２：クリーム

| | |
|---|---|
| セトステアリルアルコール | 3.5 |
| スクワラン | 40.0 |
| ミツロウ | 3.0 |
| 還元ラノリン | 5.0 |
| エチルパラペン | 0.3 |
| ポリオキシエチレン(20) ソルビタンモノパルミチン酸エステル | 2.0 |
| ステアリン酸モノグリセリド | 2.0 |
| N-ステアロイルグルタミン酸ナトリウム | 0.5 |
| 2-ヒドロキシ -4-メトキシベンゾフェノン | 0.5 |
| メトキシケイ皮酸オクチル | 1.0 |
| 酢酸レチノール | 2.0 |
| 月見草油 | 0.05 |
| 香料 | 0.03 |
| 6-(3,4- ジエチルフェニルカルボキサミド) ニコチン酸 | 0.1 |
| 1,3-ブチレングリコール | 5.0 |
| ポリエチレングリコール1500 | 5.0 |
| 精製水 | 残余 |

【００３８】セトステアリルアルコール、スクワラン、ミツロウ、還元ラノリン、エチルパラペン、ポリオキシエチレン(20)ソルビタンモノパルミチン酸エステル、ステアリン酸モノグリセリド、N-ステアロイルグルタミン酸ナトリウム、2-ヒドロキシ-4-メトキシベンゾフェノン、メトキシケイ皮酸オクチル、酢酸レチノール、月見草油、6-(3,4- ジエチルフェニルカルボキサミド) ニコチン酸を加熱溶解し、別個に 75 ℃に加温した1,3-ブチレングリコール、ポリエチレングリコール1500とともに精製水に撹拌しながら加えた。ホモミキサー処理し乳化粒子を細かくした後、撹拌しながら急冷してクリームを得た。

【００３９】

例３：乳液

| | |
|---|---|
| 6-(3,5- ジ-tert-ブチルフェニルカルバモイル) ニコチン酸 | 0.2 |
| パラジメチルアミノ安息香酸 -2-エチルヘキシル | 0.1 |
| ジパラメトキシケイ皮酸モノ -2-エチルヘキシル | 0.2 |
| ステアリン酸 | 1.5 |
| セチルアルコール | 0.5 |
| ミツロウ | 2.0 |
| ポリオキシエチレン(10)モノオレイン酸エステル | 2.0 |
| L-アルギニン | 0.3 |
| L-グルタミン酸Na | 0.02 |
| PCA-Na | 0.05 |
| ヒアルロン酸Na | 0.01 |
| プロピレングリコール | 5.0 |

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| | |
|---|---|
| グリセリン | 3.0 |
| エタノール | 3.0 |
| エチルパラベン | 0.3 |
| 香料 | 0.03 |
| カルボキシビニルポリマー | 0.12 |
| 精製水 | 残余 |

【００４０】エタノールに香料を加えて溶解した（アルコール相）。一方、精製水にL-アルギニン、L-グルタミン酸Na、PCA-Na、ヒアルロン酸Na、プロピレングリコール、グリセリン、カルボキシビニルポリマーを加えて加熱溶解して 70 ℃に保った（水相）。さらに、他の成分＊を混合して加熱溶解して 70 ℃に保った（油相）。水相に油相を加えて予備乳化を行い、ホモミキサーで均一に乳化した。この混合物に撹拌しながらアルコール相を加え、その後撹拌しながら 30 ℃に冷却して乳液を得た。

【００４１】

例４：フォームマスク

| | |
|---|---|
| 6-(3,5- ジ-tert-ブチルフェニルカルボキサミド)-ニコチン酸 | 0.02 |
| 4-tert- ブチル-4'-メトキシ－ジベンゾイルメタン | 0.5 |
| ステアリン酸 | 1.0 |
| ベヘニル酸 | 1.0 |
| 自己乳化型モノステアリン酸グリセリン | 1.5 |
| モノステアリン酸ポリオキシエチレン(5) グリセリン | 2.5 |
| バチルアルコール | 1.5 |
| 香料 | 0.05 |
| グリセリン | 5.0 |
| 1,3-ブチレングリコール | 5.0 |
| ポリエチレングリコール1500 | 3.0 |
| メチルパラベン | 0.1 |
| 水酸化カリウム | 0.15 |
| 精製水 | 残余 |
| 液化石油ガス | 6.0 |
| ジメチルエーテル | 2.0 |

【００４２】精製水にグリセリン、1,3-ブチレングリコール、ポリエチレングリコール1500、メチルパラベン、水酸化カリウムを加え、70℃に加熱溶解した。この溶液に液化石油ガス、ジメチルエーテルを除く他の成分を加※熱溶解して加え、均一に混合て容器に充填した。最後に液化石油ガス、ジメチルエーテルを噴射剤として加え、フォームマスクを得た。

【００４３】

例５：軟膏

| | |
|---|---|
| 6-(3,4- ジエチルフェニルカルバモイル) ニコチン酸 | 0.1 |
| パラジメチルアミノ安息香酸オクチル | 4.0 |
| ブチルメトキシベンゾイルメタン | 4.0 |
| 酢酸トコフェロール | 0.5 |
| パルミチン酸レチノール | 1.0 |
| ステアリルアルコール | 18.0 |
| モクロウ | 20.0 |
| ポリオキシエチレン(10)モノオレイン酸エステル | 0.25 |
| グリセリンモノステアリン酸エステル | 0.3 |
| ワセリン | 32.0 |
| 精製水 | 残余 |

【００４４】精製水を 70 ℃に保ち（水相）、一方、その他の成分を70℃で混合溶解した（油相）。水相に油相を加えてホモミキサーで均一に乳化し、その後冷却して軟膏を得た。

【００４５】(3) 試験例

例１：線維芽細胞の EGF依存性増殖に及ぼす作用

低血清下で増殖停止している線維芽細胞の増殖は増殖因子に依存しており、EGF の添加で増殖が促進され、レチノイン酸を共存させるとさらに増殖促進が行われる。そこで、本発明の皮膚外用剤の成分について、線維芽細胞

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の EGF依存性増殖に及ぼす作用について検討した。ヒト皮膚線維芽細胞(HF52)を継代して得た PDL12細胞を、5% FBS-DMEM に懸濁し、直径 3.5 cm のシャーレに植え付け(47,200 個／デッシュ)、37℃で7時間培養後、4 nM の EGFを含む 0.25% FBS-DMEM に所定濃度の被検化合物又はDMSOを加えた培地に交換して7日間培養した。蛍光法により細胞の DNA量を定量し、増殖促進率を求めた。

【００４６】結果を図1に示す。$10^{-6}$ M濃度のレチノイン酸を共存させることにより、EGF依存性増殖は40～50% 促進された。このレチノイン酸による EGF依存性増殖を指標にして、上記化合物のレチノイド作用を調べた。その結果、6-(3,4- ジエチルフェニルカルバモイル) ニコチン酸は$10^{-5}$ Mで 30%、$10^{-6}$ Mで 20%、6-(3,4- ジエチルフェニルカルボキサミド) ニコチン酸は$10^{-6}$ Mで 20%の増殖促進作用を示した。

【００４７】例2：外用によるヘアレスマウス皮膚表面形状（皮溝）の平坦化作用

レチノイン酸の外用あるいは内服により、皮膚は赤みを帯び、光沢と透明感のある状態に変化する。ヘアレスマウスで同様な現象が再現できることを利用し、その変化と対応のある定量的指標を用いて本発明の皮膚外用剤の作用をレチノイン酸と比較した。ヘアレスマウスに 0.05%、0.025%、及び 0.01%のレチノイン酸アセトン溶液、製造例に示した6-(3,4- ジエチルフェニルカルバモイル) ニコチン酸、6-(3,4-ジエチルフェニルカルボキサミド) ニコチン酸、6-(3,5-ジ-tert-ブチルフェニルカルバモイル) ニコチン酸、6-(3,5-ジ-tert-ブチルフェニルカルボキサミド) ニコチン酸の各 1% アセトン溶液、及びアセトンをそれぞれ 30 日間（5回／週）塗布し、最終塗布日の翌日にシリコン系樹脂を用いて皮膚表面のレプリカを取り、画像解析装置により皮膚表面形状の特徴を表す種々のパラメーターを求めた。

【００４８】レチノイン酸の連続塗布により、濃度依存的に赤みと光沢のある皮膚へと変化し、ヒト皮膚で認められるレチノイド皮膚様変化を生じた。この変化に対してレプリカ上では皮紋が消失し、表面が平坦化していく変化として捉えられた。画像解析パラメーターKSD(KSD=3.9 mm×3.9 mm内の輝度分布の分散）が皮溝深さと相関することが知られており（現代皮膚科学体系・年間版90B)、この値がレチノイン酸の作用とよく対応していた（表1）。製造例で得た化合物はいずれもレチノイン酸様の変化を生じ、レチノイン酸より弱いもののKSD 変化が認められた。組織所見では、いずれの被験化合物についてもレチノイン酸で観られた炎症性変化（表皮内・真皮内細胞湿潤、細胞間・細胞内浮腫、血管拡張など）は認められなかった。最も明瞭な変化は表皮肥厚であった（表2）。

【００４９】

【表1】

KSD変化(%)

| | |
|---|---|
| アセトン | 89.7% |
| 0.01%　レチノイン酸 | 79.2% |
| 0.025%　レチノイン酸 | 73.4% |
| 0.05%　レチノイン酸 | 33.6% |
| 1% 6-(3,4-ジエチルフェニルカルバモイル) ニコチン酸 | 84.5% |
| 1% 6-(3,4-ジエチルフェニルカルボキサミド) ニコチン酸 | 83.7% |
| 1% 6-(3,5-ジ-tert-ブチルフェニルカルバモイル) ニコチン酸 | 78.3% |
| 1% 6-(3,5-ジ-tert-ブチルフェニルカルボキサミド) ニコチン酸 | 76.9% |

【００５０】

※　※【表2】

表皮肥厚（μm)

| | |
|---|---|
| アセトン | 18μm |
| 0.01%　レチノイン酸 | 48μm |
| 1% 6-(3,4-ジエチルフェニルカルバモイル) ニコチン酸 | 22μm |
| 1% 6-(3,4-ジエチルフェニルカルボキサミド) ニコチン酸 | 21μm |
| 1% 6-(3,5-ジ-tert-ブチルフェニルカルバモイル) ニコチン酸 | 32μm |
| 1% 6-(3,5-ジ-tert-ブチルフェニルカルボキサミド) ニコチン酸 | 35μm |

【００５１】例3：ライノマウス皮膚に対する作用

ライノマウスの表皮には毛胞由来のケラチンを内包した卵形のう(utricle) が存在している。レチノイン酸の投与によりこの卵形のうが縮小することなどが知られている（例えば、Ashton, R.E. et al. J. Invest. Dermatol. 82, pp.632-635, 1984 など）。製造例で示した化合物について上記作用を調べた。8週齢の雌性ライノマウスの背部皮膚に所定濃度の被験化合物溶液及び担体0.1

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mlを１日あたり１回あるいは２回の割合で１週間に５日間、２週間にわたり塗布した。組織学的評価のために背部皮膚を切り出し、0.5% 酢酸を用いて表皮を真皮から分離し、光学顕微鏡観察用の表皮シートを作製した。CCD カメラを通して得られた画像データを解析し、卵形の＊

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＊う面積を求めた。結果を表３に示す。レチノイン酸は皮膚発赤が強いが、製造例で示した化合物では全く皮膚発赤が認められなかった。

【００５２】

【表３】

卵形のう面積の減少（vs担体，%）

| | 0.00001% | 0.0001% | 0.001% | 0.01% | 0.1% | 1% |
|---|---|---|---|---|---|---|
| レチノイン酸 | 77 | 59 | 15 | | | |
| 1% 6-(3,4- ジエチルフェニルカルバモイル）ニコチン酸 | | | | 90 | 87 | 60 |
| 1% 6-(3,4- ジエチルフェニルカルボキサミド）ニコチン酸 | | | | 95 | 89 | 50 |
| 1% 6-(3,5- ジ-tert-ブチルフェニルカルバモイル）ニコチン酸 | | | | 80 | 62 | 40 |
| 1% 6-(3,5- ジ-tert-ブチルフェニルカルボキサミド）ニコチン酸 | | | | 81 | 58 | 30 |

【００５３】例４：代謝性試験

レチノイン酸が人体に対し毒性を示す一因は、レチノイン酸が人体内において代謝されにくいことにある。そこで、製造例に示した２種の化合物の代謝性について以下の方法で検討した。一定量のラット肝ホモジネート(0.15M KCl水溶液で灌流脱血したラット肝25 gをpH 7のリン酸緩衝液 75 mlとホモジネートした25 %ホモジネート）※

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※を含む緩衝液に、エタノールに溶解した被験物質を加え（最終濃度$10^{-4}$ M）、経時的にHPLCで被験物質残量を定量した。結果を表４に示す。得られた結果から、本発明の化合物が体内で容易に代謝されることが示唆された。

【００５４】

【表４】

ラット肝ホモジネート中での代謝性

| 化合物 | 10分後残量(%) | 60分後残量 (%) |
|---|---|---|
| 6-(3,4- ジエチルフェニルカルバモイル）ニコチン酸 | 65 | 5.0 |
| 6-(3,4- ジエチルフェニルカルボキサミド）ニコチン酸 | 55 | 3.0 |

＊ t = 0 を 100 %とする。

【００５５】例５：安定性試験

製造例で得た各化合物の 300 ppmエタノール溶液にキセノン光を 30 時間照射後、及び 50 ℃で２カ月保存後の残存量を HPLC により定量した結果、いずれの化合物も 95%以上残存していることが確認された。一方、同条件下において、レチノイン酸は速やかに分解した。

【００５６】

【発明の効果】本発明の皮膚外用剤の成分である上記式の化合物は、優れた皮膚劣化防止作用を有しており、加えて、安定で経皮吸収が少なく安全性が高い。また、体内に吸収された場合にも容易に代謝されるのでレチノイド作用による副作用を引き起こすことがないという特徴を有している。

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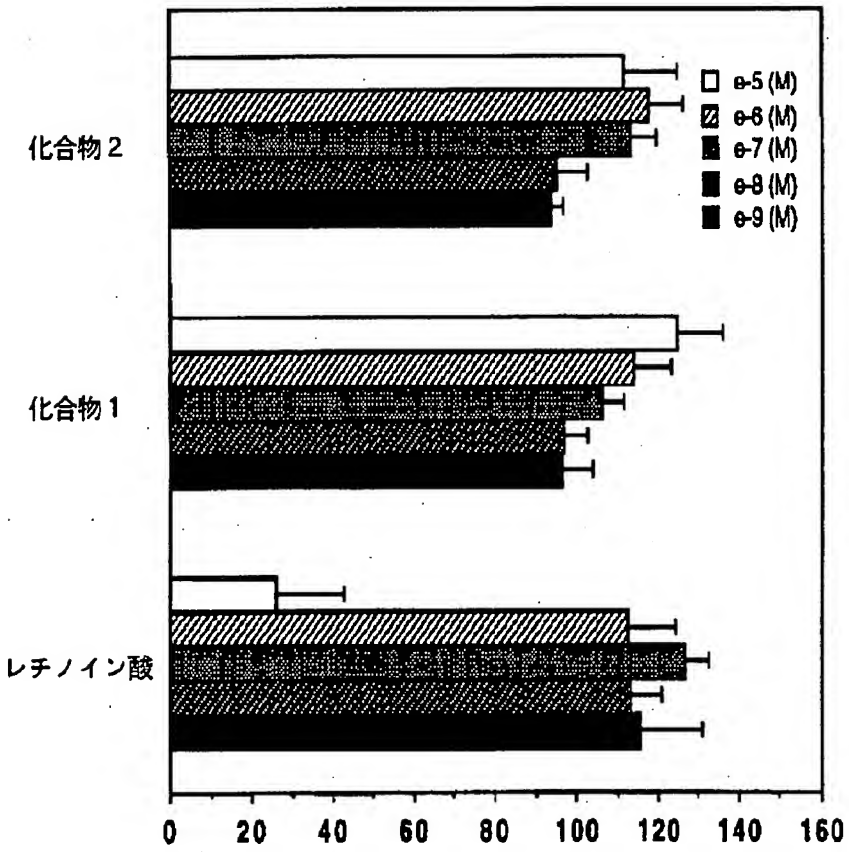
【図面の簡単な説明】

【図１】　本発明の皮膚外用剤に含まれる代表的化合物の線維芽細胞 EGF依存性増殖に及ぼす作用を示す図である。図中、化合物１は6-(3,4- ジエチルフェニルカルバモイル）ニコチン酸を示し、化合物２は6-(3,4- ジエチルフェニルカルボキサミド）ニコチン酸を示す。

【図１】

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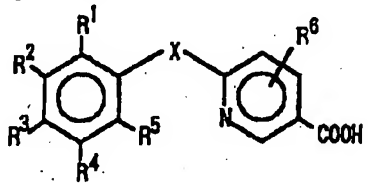
**(57) (Abstract)**

**(Construction)**

A topical agent containing a compound represented by the following formula (wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group and the like, and X denotes -NH-CO- or -CO-NH-, and R6 denotes hydrogen, 1-6C alkyl group and the like)



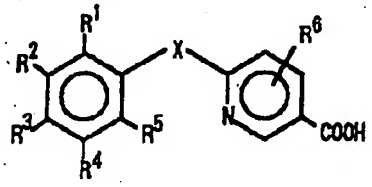
**(effect)**

It has excellent skin deterioration prevention action, and is stable with small percutaneous absorption, safety is high. Moreover, because it is readily metabolised, side effects due to retinoid action is small.

**Patent Claims**

**[Claim 1]**

A topical agent containing a compound represented by the following formula:



(wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group, X denotes -NH-CO- or -CO-NH-, and R6 denotes hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group).

**[Claim 2]**

A topical agent in accordance with Claim 1, having skin deterioration prevention action.

**[Claim 3]**

A topical agent in accordance with Claim 1, wherein aforesaid compound is a compound that is not substantially absorbed percutaneously.

**[Claim 4]**
A topical agent in accordance with the Claim 1, wherein the local and/or systemic cytotoxicity is reduced.

**[Claim 5]**
A skin deterioration inhibitor for topical use, containing a compound in accordance with Claim 1 as effective ingredient.

**(Detailed Description of the Invention )**
(0001)
(Sphere of Application in Industry)
This invention is related to a topical agent, in particular, a topical agent having skin deterioration prevention action.

(0002)
(Technology of the Prior Art)
In order to prevent skin deterioration such as wrinkling, sagging of skin and disappearance of brightness accompanying the photo-damage due to sun irradiation or aging, various topical agents have been used. In such topical agents, a component that protects the skin from the external factor such as sun, a component that acts on the skin itself and promotes activation of skin, and the like are formulated. As an effective ingredient having the latter action, Vitamin A or derivatives thereof are attracting attention.

(0003)
It is known that the retinoic acid which is an active metabolite of vitamin A (vitamin A acid) binds to a specific receptor of the target cell, and physiological effect is displayed, and the compound which binds to this receptor (retinoid receptor) and displays retinoic acid-like action is generally known generally as retinoid. Moreover, it is known that retinoid has various kinds of actions such as vision control action, growth stimulation action, reproduction action and the like, and in particular it plays an important function for the normal differentiation and maintenance of skin. In some cases, topical agent containing vitamin A and some retinoids may be topically used for the purpose of skin deterioration prevention. However, in practice, whether a rough skin, dryness, follicular hyperkeratosis and the like are inhibited by retinoid or not, or whether the effective for skin deterioration prevention or not, is not known.

(0004)
On the other hand, the retinoids sometimes used for aforesaid purpose, in general have a highly lipid soluble characteristics, and when applied as a topical agent, they are quickly absorbed to the body from the skin (percutaneous absorption), and there is a situation that systemic side effect such as hyperretinoidosis and the like are accompanied in addition to the target topical action (skin deterioration prevention action). Moreover, these retinoids were not readily decomposed locally and in vivo, and there was case that side effect due to cell injury is induced, and there are many restrictions for the application for the purpose of skin deterioration prevention.

(0005)
On the other hand, as compound having retinoid action, benzoic acid derivatives in accordance with Kokai 61-22047, Kokai 61-76440 are known. Moreover, pyridine carboxylic acid derivatives having retinoid action are disclosed in Kokai 6-263702, EP Laid-Open 617020-A1 and PCT WO93/6086. As for pyridine carboxylic acid derivatives disclosed in Kokai 6-263702 EP Laid-Open 617020-A1, usefulness as anti bone disease medicine is known as well (Kokai 7-17854), however, it has not been suggested or indicated in any of these publications that these derivatives have skin deterioration prevention action.

(0006)
As for the pyridine carboxylic acid derivatives disclosed in PCT WO93/6086, it is indicated in said publication that it is useful for therapy of dermatosis, however, there is no suggestion nor indication that these derivatives have skin deterioration prevention action. Moreover, these pyridine carboxylic acids have 5,5,8,8-tetramethyl-5,6,7,8-tetrahydro naphthyl group or 3-adamantyl phenyl group, and has an extreme lipid soluble characteristic.

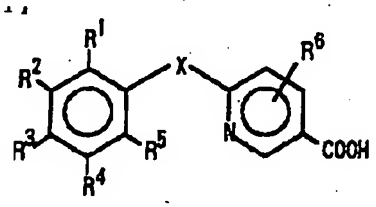
(Problems to be Overcome by this Invention)
The object of this invention is to put forward a topical agent which has excellent skin deterioration prevention action. In a further embodiment, the object of this invention is to put forward aforesaid topical agent, wherein a compound having retinoic acid action is contained as effective ingredient, and cytotoxicity is reduced. Moreover, another object of this invention is to put forward a topical agent having excellent skin deterioration prevention action which has no systemic side effect such as hyperretinoidosis.

(0007)
(Means to Overcome these Problems)

These inventors carried out assiduous investigations in order to solve aforesaid problem, as a result, discovered that nicotinic acid derivatives of the following formula having activity of retinoic acid had extremely excellent skin deterioration prevention action. Moreover, these inventors also discovered that these compounds were comparatively hydrophilic, had little percutaneous absorption properties, and also were readily decomposed on skin and in vivo, therefore systemic cytotoxicity was remarkably reduced. This invention was completed on the basis of aforesaid findings.

(0008)

In other words, this invention puts forward a topical agent containing a compound represented by the following formula:




(wherein, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group, X denotes -NH-CO- or -CO-NH-, and R6 denotes hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group).

(0009)

In accordance with the preferred form of aforesaid invention, aforesaid topical agent having skin deterioration prevention action, aforesaid topical agent wherein, aforesaid compound is a compound which is not substantially absorbed percutaneously, and aforesaid topical agent wherein topical and/or systemic cytotoxicity is reduced, are put forward. Moreover, in accordance with another form of this invention, a skin deterioration inhibitor for topical use containing aforesaid compound as effective ingredient is put forward.

(0010)

In aforesaid compound contained in topical agent of this invention, R1, R2, R3, R4 and R5 each independently denote hydrogen, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group. As C1-6 alkyl group, either of straight chain or branched alkyl group may be used, and as further example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, sec-butyl group, tert butyl group, n-pentyl group, iso pentyl group, neopentyl group, n-hexyl group and the like can be used. Among these, ethyl group, isopropyl group or tert butyl group is preferably used. As C1-6 alkoxy group, either of straight or branched chain alkoxy group may be used, and as a

further example, methoxy group, ethoxy group, n-propoxy group, isopropoxy group, n-butoxy group, sec-butoxy group, tert butoxy group and the like can be used. As halogen atom, any of fluorine atom, chlorine atom, bromine atom or iodine atom may be used.

(0011)
For example, among such compounds, a compound in which two adjacent or non-adjacent substituents selected from the aforesaid R1, R2, R3, R4 and R5 are same or different alkyl groups is a preferred compound as the component of topical agent of this invention. For example, a compound in which R2 and R3, or R2 and R4 are both alkyl groups is preferred. Among such compounds, the compound wherein the alkyl group is ethyl group, isopropyl group or tert butyl group is more preferred, and methylene group is particularly preferred.

(0012)
R6 denotes hydrogen atom, 1-6C alkyl group, hydroxy group, halogen atom or C1-6 alkoxy group. As C1-6 alkyl group, halogen atom or C1-6 alkoxy group, aforesaid species can be used. R6 can be substituted at arbitrary position of 2-position, 5-position or 6-position of pyridine ring. Among these the compound in which R6 is hydrogen atom is preferred.

(0013)
In more concrete terms, as component of topical agent of this invention, compounds such as 6-(3,4-diethylphenyl carbamoyl) nicotinic acid, 6-(3,4-diethylphenyl carboxamide) nicotinic acid, 6-(3,5-di-t-butylphenyl carbamoyl) nicotinic acid or 6-(3,5-di-t-butylphenyl carboxamide) nicotinic acid and the like are preferred, but the component of topical agent of this invention is not restricted to these preferred compounds. Moreover, in topical agent of this invention, one or more of aforesaid compounds can be used in a combination thereof. Moreover, arbitrary base addition salt and arbitrary hydrate of aforesaid compound may be used. For example, as base addition salt, sodium salt, metal salt such as potassium salt, calcium salt, magnesium salt and ammonium salt, organic amine salt and the like can be used.

(0014)
The quantity formulated of the aforesaid compound is not restricted in particular in topical agent of this invention, and it can be suitably varied depending on the type of the compound, application purpose and the state of skin, but in general it is 0.005-5.0 wt.% in total quantity of topical agent, preferably 0.05-1.0 wt.%. Moreover, in general, if the quantity formulated of aforesaid compound is less than 0.005 wt.%, there is a situation that the effect is not sufficient, and moreover even when the

quantity formulated exceeds 5.0 wt.%, the enhancement of the potentiation of skin deterioration prevention effect is not observed in some cases, therefore, it is not preferred to be greatly deviated from aforesaid range.

(0015)
A part of the aforesaid compound is well known compound, and for example, it can be readily produced by the method described in Kokai 6-263702 and EP Laid-Open 617020-A1. Moreover, the novel compounds can be readily produced by a person skilled in the art in accordance with processes in Examples of this specification or in aforesaid publication, furthermore by referring to process in accordance with publications such as Kokai 7-17854 and PCT WO 93/6086 in addition to these.

(0016)
In addition to aforesaid to topical agent of this invention, other components used for topical agent such as usual cosmetics, pharmaceutical agent, over the counter drug and the like, can be used. For example, vitamin B2 species such as riboflavin, riboflavin butyrate, flavin adenine dinucleitide and the like, vitamin B6 species such as pyridoxine hydrochloride, pyridoxine dioctanoate and the like, vitamin C species such as L-ascorbic acid, L-ascorbic acid dipalmitate, L-ascorbic acid-2-sodium sulphate and the like, pantothenic acid species such as calcium pantothenate, D-pantotenyl alcohol, pantotenyl ethyl ether, acetyl pantotenyl ethyl ether and the like, vitamin D species such as ergocalciferol, cholecalciferol and the like, nicotinic acid species such as nicotinic acid, nicotinamide, benzyl nicotinate and the like.

(0017)
vitamin E species such as alpha-tocopherol, tocopherol acetate, DL-alpha-tocopherol nicotinate, DL-alpha-tocopherol succinate and the like, vitamin species such as vitamin P, biotin and the like, amino acids and amino acid derivatives such as glycine, alanine, valine, leucine, isoleucine, serine, threonine, aspartic acid and salts thereof, glutamic acid and salts thereof, lysine, arginine, cysteine, cystine, methionine, phenylalanine, tyrosine, histidine, tryptophan, proline, N-acyl acidic amino acid salt such as N-palmitoyl L-aspartic acid diethyl, N-coconut oil fatty acid-L-sodium glutamate and the like, acyl neutral amino acid salt such as coconut oil fatty acid sarcosine triethanolamine, lauroyl methyl-beta-alanine sodium and the like, pyrrolidone carboxylic acid and salts thereof, POE(40) hardened castor oil mono pyroglutamate mono iso stearic acid diester, N-coconut oil fatty acid -L-arginine ethylester -DL-pyrrolidone carboxylic acid salt and the like.

(0018)

Oil such as avocado oil, palm oil, peanut oil, beef tallow, rice bran oil, jojoba oil, evening primrose oil, carnauba low, lanolin, liquid paraffin, squalane, palmitic acid iso stearyl, iso stearyl alcohol, tri-2-ethyl hexanoic acid glycerol and the like, moisturizing agent such as glycerine, sorbitol, polyethyleneglycol, 1,3-butylene glycol, collagen, hyaluronic acid, chondroitin sulfate, dextran sulfate sodium and the like, antioxidant such as sodium erythorbate, para hydroxyanisole and the like, detergent such as stearyl sodium sulfate, cetyl sulfuric acid diethanolamine, cetyltrimethylammonium saccharin, iso stearic acid polyethyleneglycol, arachic acid glyceryl, diglycerol di iso stearate, phospholipid and the like, preservatives such as ethylparaben, butyl para pen and the like.

(0019)
Antiphlogistic such as glycyrrhizin acid derivative, glycyrrhetinic acid derivative, salicylic acid derivative, hinokitiol, zinc oxide, allantoin and the like, beautfiying and whitening agent such as placenta extract, glutathione, Saxifraga extract and the like, extract such as Phellodendron, Coptis, Shikon, peony, sialid, birch, sage, loquat, carrot, aloe, Malva sylvestris, iris, grape, coix, sponge gourd, lily, saffron, Cnidium officinale, ginger, Hypericum erectum, Ononis, rosemary, garlic and the like, activator such as a royal jelly, photo sensitive element, cholesterol derivatives, calf blood extract and the like, blood circulation accelerating agent such as gamma-oryzanol and the like, anti-seborrhoica agent such as sulphur, thianthol and the like, thickener such as carboxy vinyl polymer, carboxymethylcellulose, carboxy hydroxypropylcellulose and the like, flavour, water, alcohol, colour agent such as titanium yellow, casamine, safflower red and the like, or resin powder such as polyethylene, nylon and the like. These can be suitably formulated in accordance with requirements.

(0020)
An effective ingredient of drug useful for prevention and treatment of dermatosis and/or UV absorbent useful for prevention of photo damage and the like may be formulated to the topical agent of this invention. As effective ingredient of such drug, for example, steroidal compound and antibiotics and the like are nominated. As UV absorbent, cinnamic acid series UV absorbent such as para methoxy cinnamic acid-2-ethoxyethyl, para methoxy cinnamic acid isopropyl ester, diisopropyl cinnamate, para methoxy cinnamic acid ethylhexyl, dipara methoxy cinnamic acid mono -2-ethyl hexanoic acid glyceryl, methoxy cinnamic acid octyl and the like, benzoyl methane series UV absorbent such as butyl methoxybenzoyl methane, 4-tert butyl-4'-methoxy-dibenzoyl-methane and the like, benzophenone series UV absorbent such as glyceryl-mono-2-ethyl hexanoyl-di-para methoxybenzophenone, 2,2'-dihydroxy-4-methoxybenzophenone, 2,2'-dihydroxy-4,4'-dimethoxy

benzophenone, 2-hydroxy-4-methoxybenzophenone, 2-hydroxy-4-methoxybenzophenone-5-sodium sulphonate and the like can be used.

(0021)

Benzoate system UV absorbent such as ortho aminobenzoic acid methyl ester, para dimethylaminobenzoic acid -2-ethylhexyl ester, para dimethylaminobenzoic acid octyl ester and the like, benzoate system UV absorbent such as glyceryl p-amino benzoate, amyl-para-dimethylamino benzoate, ethyl-4-bis hydroxypropyl amino benzoate and the like, other UV absorbent such as 2-ethylhexyl -2-cyano-3,3'-diphenyl acrylate, digalloyl trioleate, salicylic acid-2-ethylhexyl, salicylic acid homo methyl, guaiazulene, urocanic acid and the like can be sued.

(0022)

Topical agent of this invention has an action of preventing the skin deterioration such as wrinkling, sagging of skin and disappearance of brightness accompanying the photo-damage due to sun irradiation or aging. Accordingly, by applying topical agent of this invention to the daily repair of skin and after sunbathing, deterioration of skin can be prevented, and youthful and healthy state of skin can be maintained. Moreover, agent form of topical agent of this invention is not restricted in particular, and for example agent forms such as solubilisation system such as toner and the like, emulsification system such as milky lotion, cream and the like, or ointment, dispersant, aerosol can be formed. Method of use is not restricted in particular, however, in the case of formulation such as cream agent, a suitable quantity is taken with a finger, and it is applied thinly and thoroughly to face and hand and preferably if it is rubbed into skin by massaging. Below, this invention is further described in concrete terms by Example, however, this invention is not restricted to these Examples.

(0023)

**(Examples)**

**(1) Production of compound.**

Example 1: 6-(3,4-diethylphenyl carbamoyl) nicotinic acid.

A liquid mixture of concentrated sulfuric acid 8.1 ml and nitric acid (d = 1.42) 5.16 ml was dropwise-added at 0 degrees to 1,2-diethylbenzene 9.96 g (74.3 mmol) and it was reacted at the same temperature for two hours. The reaction liquor was discharged into ice, and extraction was carried out with ether. The organic layer was washed with water 3 times, with saturated aqueous sodium bicarbonate and with saturated aqueous sodium chloride solution in this order, and the solvent was

eliminated by distillation after dehydration. The residue was purified by silica gel column chromatography (Fuji silica, BW-820MH, 500 g, eluent n-hexane / methylene chloride = 19/1), and 3,4-diethyl nitrobenzene 7.8 g was obtained (yield = 58.6 %). Aforesaid 3,4-diethyl nitrobenzene 6 g (36 mmol) and 5 % Pd/c 0.6 g were added to ethanol 100 ml, and catalytic reduction was carried out at normal temperature and normal pressure. The catalyst was eliminated by filtration, thereafter the solvent was eliminated by distillation, and 3,4-diethylamino benzene 4.89 g was obtained (yield: 91.2 %).

(0024)

3-methoxycarbonyl pyridine-2-carboxylic acid 4.62 g (25 mmol) was added to anhydrous benzene 500 ml and thionyl chloride 77 ml and it was reacted for six hours under reflux. The solvent was eliminated by distillation, anhydrous benzene 100 ml was added to the residue, and thionyl chloride was azeotropically-concentrated (three times). Anhydrous benzene 385 ml was added to the residue and dissolution caused, and 3,4-diethylamino benzene 4.5 g (25 mmol) dissolved in dried pyridine 19.2 ml and anhydrous benzene 385 ml was dropwise added to this solution and mixed at room temperature, and it was reacted for three hours under a stream of argon. The reaction liquor was added to iced water 1925 ml, 2 N HCl 77 ml was added and stirred well, and it was extracted three times with ethyl acetate 1.2 l. The organic layer was washed with saturated aqueous sodium chloride solution 1.2 l, thereafter it was dried with magnesium sulfate, and it was concentrated and dried to a solid. The residue was purified by silica gel column chromatography (Fuji silica, BW-820MH, 500 g, eluent ethyl acetate / n-hexane = 1/3), and crude product 7.57 g was obtained. The obtained product was recrystallised from n-hexane / ethyl acetate, and 6-(3,4-diethylphenyl carbamoyl) nicotinic acid methyl ester 6.35 g was obtained (yield: 81.4 %).

(0025)

6-(3,4-diethylphenyl carbamoyl) nicotinic acid methyl ester 6 g (19.2 mmol) was dissolved in methanol 1 l, and 2 N NaOH 200 ml was added and reacted at room temperature for 12 hours. The reaction liquor was added to 0.5 N HCl 1.2 litre and extracted three times with ethyl acetate 1.2 l. The organic layer was washed with saturated aqueous sodium chloride solution 1.2 l, thereafter dried with magnesium sulfate, and solvent was eliminated by distillation. The residue was recrystallised from ethyl acetate / ethanol, and 6-(3,4-diethylphenyl carbamoyl) nicotinic acid 2.9 g was obtained (yield: 50.7 %).

Straw-coloured needle-like crystal, mp 174-176 degrees.

1H NMR (400 MHz, DMSO-d6, 30 degrees) delta: 10.57 (s, 1H), 9.16 (d, 1H, J = 2 Hz), 8.50 (dd, 1H, J = 2 Hz, 8 Hz), 8.25 (d, J = 8 Hz), 7.71 (d, 1H, J = 2 Hz), 7.67 (dd, 1H, J = 2 Hz, 8 Hz), 7.14 (d, J = 8 Hz), 2.61 (m, 4H), 1.19 (t, 3H, J = 7.5 Hz), 1.16 (t, 3H, J = 7.5 Hz)
Elemental analysis (C17H18N2O3): theoretical value C 68.44; H 6.08; N 9.39, experimental value C 68.70; H 6.11; N 9.41.

(0026)
Example 2:. 6-(3,4-diethylphenyl carboxamide) nicotinic acid.
nitromethane solution (60 ml) of acetyl chloride 6.44 g (82.0 mmol) and 1,2-diethylbenzene 9.50 g (70.8 mmol) was added dropwise into nitromethane solution (60 ml) of aluminium chloride (AlCl3) 11.4 g (62.2 mmol) and mixed at 0 degrees over a period of one hour. The reaction liquor was stirred at room temperature for two hours, and it was discharged into iced water 150 ml. Ethyl acetate 150 ml was added to this mixture, it was filtered with celite, and the aqueous layer was extracted with ethyl acetate (100 ml). The ethyl acetate layer was recovered, washed successively with water, saturated aqueous sodium bicarbonate, water and saturated aqueous sodium chloride solution (for each 100 ml), thereafter it was dried with sodium sulfate and the solvent was eliminated by distillation. Vacuum distillation (bp 95 degrees /1.2 mm Hg) was carried out of the residue, and 3,4-diethyl acetophenone 12.0 g was obtained (yield: 96 %).

(0027)
Mixed liquor of 5% NaOCl solution (275 ml) and 25% NaOH solution (33 ml) was added dropwise and mixed to dioxane (160 ml) solution of 3,4-diethyl acetophenone 11.0 g (62 mmol) and it was reacted at 50-60 degrees for two hours. The reaction liquor was cooled and discharged into iced water 1 l, and NaHSO3 was added and thereafter it was adjusted to pH 3 with concentrated hydrochloric acid. This mixture was extracted with ethyl acetate (750 ml, 500 ml). The ethyl acetate layer was washed with water and saturated aqueous sodium chloride solution (for each 500 ml), dried with sodium sulfate, and the solvent was eliminated by distillation. Obtained crude product 11.0 g was recrystallised from n-hexane 120 ml, and 3,4-diethyl benzoic acid 10.2 g was obtained (yield: 92 %).

(0028)
Thionyl chloride 28 ml was added to anhydrous benzene (200 ml) solution of 3,4-diethyl benzoic acid 6.5 g (36.5 ml) and it was reacted under reflux for five hours. The reaction liquor was concentrated, thereafter it was substituted twice with anhydrous benzene 50 ml and it was concentrated. Dried THF 25 ml was added to the residue and dissolved, and this solution was added

dropwise and mixed at room temperature to dried THF solution (300 ml) of 6-amino nicotinic acid methyl ester 5.55 g (36.5 ml) and triethylamine 4.61 g (4.56 mmol). The reaction liquor was stirred at room temperature for three hours. The reaction liquor was concentrated, and ethyl acetate (150 ml) and water (100 ml) were added. The aqueous layer was extracted with ethyl acetate (50 ml x 2), ethyl acetate layer was washed with water and saturated aqueous sodium chloride solution (100 ml each), it was dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography (BW-820MH, 300 g, eluent methylene chloride / ethyl acetate = 15/1), and 9.0 g mixture of 6-(3,4-diethylphenyl carboxamide) nicotinic acid methyl ester and diamide body was obtained.

(0029)

This mixture was dissolved in methanol (650 ml), concentrated hydrochloric acid (20 ml) was added and it was reacted at 55 degrees for two hours 30 minutes. The reaction liquor was concentrated, saturated aqueous sodium bicarbonate (400 ml) and methylene chloride (200 ml) were added, and the aqueous layer was extracted with methylene chloride (150 ml, 100 ml). The methylene chloride layer was washed with water, dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography (BW-820MH, 250 g, eluent benzene / acetone = 30/1), and crude product 5.5 g was obtained. This product was recrystallised from n-hexane (100 ml), and 6-(3,4-diethylphenyl carboxamide) nicotinic acid methyl ester 4.7 g was obtained (yield: 41 %).

(0030)

6-(3,4-diethylphenyl carboxamide) nicotinic acid methyl ester 4.7 g (15 mmol) was dissolved in methanol (900 ml) and 2 N NaOH 170 ml was added and reacted at room temperature for 12 hours. The reaction liquor was added to 0.5 N HCl (1270 ml) and extracted with ethyl acetate (6 l, 2 l) The organic layer was washed with saturated aqueous sodium chloride solution (2 l), thereafter it was dried with sodium sulfate, and solvent was eliminated by distillation. The residue was recrystallised from chloroform / ethanol = 1/1 (720 ml), and 6-(3,4-diethylphenyl carboxamide) nicotinic acid 2.4 g was obtained (yield: 54 %).

Colourless needle-like crystal, mp 294-295 degrees.

1H NMR (400 MHz, DMSO-d6, 30 degrees) delta: 11.02 (s, 1H), 8.88 (m, 1H), 8.32 (br d, 1H, J = 8 Hz), 8.30 (dd, 1H, J = 2 Hz, 8.8 Hz), 7.88 (d, 1H, J = 2 Hz), 7.82 (dd, 1H, J = 2 Hz, 8 Hz), 7.30 (d, 1H, J = 8 Hz), 2.69 (q, 4H, J = 7.5 Hz), 1.23 (t, 3H, J = 7.5 Hz), 1.19 (t, 3H, J = 7.5 Hz), 1.23 (t, 3H, J = 7.5 Hz), 1.19 (t, 3H, J = 7.5 Hz) z

Elemental analysis (C17H18N2O3): theoretical value C 68.44; H 6.08; N 9.39, experimental value C 68.25; H 6.08; N 9.10.

(0031)

Example 3: 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid.

A mixture of 3,5-di-tert-butyl benzoic acid (1,800 mg), thionyl chloride (3 ml) and anhydrous benzene (20 ml) was refluxed for six hours. Solvent and excess thionyl chloride were distilled under reduced pressure. The residue was dissolved in anhydrous benzene (15 ml) and a mixture of 6-amino nicotinic acid methyl (500 mg), triethylamine (3 ml), anhydrous benzene (10 ml) was added and it was reacted at room temperature overnight. The reaction liquor was introduced into water, and extraction was carried out with ethyl acetate. The organic layer was washed with water and dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography, and a mixture (770 mg) of 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid methyl ester and diacyl body was obtained. This mixture was dissolved in methanol (30 ml), concentrated hydrochloric acid (1 ml) was added and it was refluxed for three hours. The solvent was eliminated by distillation, and methylene chloride and 1 N aqueous sodium bicarbonate were added to the residue. The organic layer was washed with water, dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was purified by silica gel column chromatography, and 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid methyl ester was obtained.

(0032)

6-(3,5-di-tert-butylphenyl carboxamide) methylnicotinate (93 mg) was dissolved by heating to methanol (10 ml). 2 N NaOH (2 ml) was added, and the reaction liquor was stirred at room temperature overnight. The reaction liquor was acidified by adding 2 N HCl and thereafter solvent was eliminated by distillation. To the residue were added ethyl acetate and water, the organic layer was separated and was washed with saturated aqueous sodium chloride solution, dried with sodium sulfate, and the solvent was eliminated by distillation. The residue was recrystallised from methanol / ethyl acetate, and 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid was obtained.

Colourless prism crystals, mp >300 degrees.

1H NMR (400 MHz, DMSO-d6, 30 degrees) delta: 11.27 (s, 1H), 8.89 (d, 1H, J = 2.2 Hz), 8.34 (d, 1H, J = 8.4 Hz), 8.31 (dd, 1H, J = 2 Hz, 8.5 Hz), 7.87 (d, 1H, J = 1.5 Hz), 7.63 (brt, 1H), 1.34 (s, 18H)

Elemental analysis (C21H26N2O3): theoretical value C 71.16; H 7.39; N 7.90, experimental value C 71.19; H 7.66; N 7.88.

(0033)

Example 4: 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid.

5-methoxycarbonyl pyridine-2-carboxylic acid (14 g) was dissolved in benzene (120 ml) and thionyl chloride (85 ml) was added, and it was refluxed for four hours. The solvent was eliminated by distillation, anhydrous benzene was added to the residue, thionyl chloride was eliminated by distillation and acid chloride was obtained. Benzene solution of aforesaid acid chloride (170 ml) was dropwise-added at 20 degrees to pyridine (62 ml) - benzene (100 ml) solution of 3,5-di-tert-butyl aniline (14.9 g) and it was reacted for three hours. The reaction liquor was discharged into iced water (120 ml), 1 N HCl (57 ml) was added and it was extracted twice with ethyl acetate (60 ml). The organic layer was washed successively with 0.5 N HCl (150 ml) and saturated aqueous sodium chloride solution (150 ml x twice), and it was dewatered with anhydrous magnesium sulphate. It was treated with activated charcoal (850 mg), and the solvent was eliminated by distillation, and 26.8 g residue was obtained. It was recrystallised from mixed solvent of n-hexane and ethyl acetate, and ester of 22.5 g was obtained.

(0034)

Aforesaid ester was suspended in methanol (280 ml), and 2 N NaOH (125 ml) was added at 20 degrees or less and it was reacted at room temperature for six hours. 1.5 N HCl (150 ml) was added at 20 degrees or less and precipitated crystals were extracted with ethyl acetate 1.5 l. After washing, ethyl acetate was eliminated by distillation and residue was recrystallised from ethyl acetate - ethanol, and 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid 14.7 g was obtained. mp. 288-289.5 degrees.

(0035)

**(2) Production Example of topical agent.**

Example 1: Toner.

| | |
|---|---|
| 6-(3,4-diethylphenyl carbamoyl) nicotinic acid | 0.05 |
| 2-hydroxy -4-methoxybenzo phenone-5-sodium sulphonate | 0.1 |
| Acetic acid tocophenol | 0.01 |
| Glycerine | 4.0 |
| 1, 3-butylene glycol | 4.0 |
| Ethanol | 8.0 |
| Polyoxyethylene (60) hardened castor oil | 0.5 |
| Methyl para pen | 0.2 |
| Citric acid | 0.05 |
| Citric acid soda | 0.1 |

| | |
|---|---|
| Flavour | 0.05 |
| Purified water | balance |

(0036)

2-hydroxy-4-methoxybenzo phenone-5-sodium sulphonate, citric acid, citric acid soda, glycerine and 1,3-butylene glycol were dissolved in purified water. Separately, polyoxyethylene (60) hardened castor oil, acetic acid tocophenol, flavour and methyl paraben were dissolved to 6-(3,4-diethylphenyl carbamoyl) nicotinic acid and ethanol, and this solution was added to aforesaid solution and a toner was obtained by filtration.

(0037)

Example 2: cream.

| | |
|---|---|
| Cetostearyl alcohol | 3.5 |
| Squalane | 40.0 |
| Beeswax | 3.0 |
| Reduction lanolin | 5.0 |
| Ethylparaben | 0.3 |
| Polyoxyethylene (20) sorbitan mono palmitate | 2.0 |
| Stearic acid monoglyceride | 2.0 |
| N-stearoyl sodium glutamate | 0.5 |
| 2-hydroxy -4-methoxybenzo phenone | 0.5 |
| Methoxy cinnamic acid octyl | 1.0 |
| Retinol acetate | 2.0 |
| Evening primrose oil | 0.05 |
| Flavour | 0.03 |
| 6-(3,4-diethylphenyl carboxamide) nicotinic acid | 0.1 |
| 1,3-butylene glycol | 5.0 |
| Polyethyleneglycol 1500 | 5.0 |
| Purified water | balance |

(0038)

Cetostearyl alcohol, squalane, beeswax, reduction lanolin, ethylparaben, polyoxyethylene (20) sorbitan mono palmitate, stearic acid monoglyceride, N-stearoyl sodium glutamate, 2-hydroxy-4-methoxybenzo phenone, methoxycinnamic acid octyl, retinol acetate, evening primrose oil and 6-(3,4-diethylphenyl carboxamide) nicotinic acid were dissolved by heating, and this was added while stirring to purified water together with 1,3-butylene glycol and polyethyleneglycol 1500 which were separately warmed to 75 degrees. It was processed with a homo mixer, the emulsified particles were made fine, thereafter it was rapidly cooled while stirring, and cream was obtained.

(0039)

Example 3: Milky lotion

| | |
|---|---|
| 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid | 0.2 |
| Para dimethylaminobenzoic acid -2-ethylhexyl | 0.1 |
| Dipara methoxy cinnamic acid mono -2-ethylhexyl | 0.2 |
| Stearic acid | 1.5 |
| Cetyl alcohol | 0.5 |
| Beeswax | 2.0 |
| Polyoxyethylene (10) monoolein acid ester | 2.0 |
| L-arginine | 0.3 |
| L-glutamate Na | 0.02 |
| PCA-Na | 0.05 |
| Hyaluronate Na | 0.01 |
| Propylene glycol | 5.0 |
| Glycerine | 3.0 |
| Ethanol | 3.0 |
| Ethylparaben | 0.3 |
| Flavour | 0.03 |
| Carboxy vinyl polymer | 0.12 |
| Purified water | balance. |

(0040)

Flavour was added to ethanol and was dissolved (alcohol phase). On the other hand, L-arginine, L-glutamate Na, PCA-Na, hyaluronate Na, propylene glycol, glycerol, carboxy vinyl polymer were added to purified water and were dissolved by heating, and it was held at 70 degrees (aqueous phase). Furthermore, other components were mixed and dissolved by heating, and it was kept at 70 degrees (oil phase). The oil phase was added to the aqueous phase, preliminary emulsification was carried out, and it was uniformly emulsified with a homo mixer. While stirring this mixture, alcohol phase was added, thereafter it was cooled to 30 degrees while stirring, and amilky lotion was obtained.

(0041)

Example 4: foam mask.

| | |
|---|---|
| 6-(3,5-di-tert-butylphenyl carboxamide)-nicotinic acid | 0.02 |
| 4-tert butyl-4'-methoxy-dibenzoyl-methane | 0.5 |
| Stearic acid | 1.0 |
| Behenic acid | 1.0 |
| Self emulsification type monostearic acid glycerol | 1.5 |
| Monostearic acid polyoxyethylene (5) glycerol | 2.5 |
| Batyl alcohol | 1.5 |
| Flavour | 0.05 |
| Glycerine | 5.0 |
| 1,3-butylene glycol | 5.0 |
| Polyethyleneglycol 1500 | 3.0 |
| Methylparaben | 0.1 |
| Potassium hydroxide | 0.15 |
| Purified water | balance |
| Liquefied petroleum gas | 6.0 |
| Dimethylether | 2.0. |

(0042)

Glycerol, 1,3-butylene glycol, polyethyleneglycol 1500, methylparaben, potassium hydroxide were added to purified water and dissolved by heating at 70 degrees. Other components except for liquefied petroleum gas and dimethylether were dissolved by heating and added to this solution, it was uniformly mixed, and packed into a container. Finally liquefied petroleum gas and dimethylether were added as propellant, and foam mask was obtained.

(0043)

Example 5: ointment.

| | |
|---|---|
| 6-(3,4-diethylphenyl carbamoyl) nicotinic acid | 0.1 |
| Para dimethylaminobenzoic acid octyl | 4.0 |
| Butyl methoxybenzoyl methane | 4.0 |
| Tocopheryl acetate | 0.5 |
| Palmitic acid retinol | 1.0 |
| Stearyl alcohol | 18.0 |
| Japan wax | 20.0 |
| Polyoxyethylene (10) monoolein acid ester | 0.25 |
| Glycerol monostearic acid ester | 0.3 |
| Vaseline | 32.0 |
| Purified water | balance. |

(0044)

Purified water was kept at 70 degrees (aqueous phase), on the other hand, other components were mixed and dissolved at 70 degrees (oil phase). The oil phase was added to aqueous phase, it was uniformly emulsified with a homo mixer, thereafter it was cooled, and ointment was obtained.

(0045)

**(3) Test examples.**

Example 1: Action on EGF dependent proliferation of fibroblast.

Proliferation of fibroblast whose proliferation is arrested under low serum condition, is dependent on the growth factor, and the proliferation is promoted with addition of EGF, and when retinoic acid is caused to be co-present further proliferation promotion is performed. Therefore the action on EGF dependent proliferation of fibroblast was examined with respect to the component of topical agent of this invention. PDL12 cells obtained by subculturing human skin fibroblast (HF52) was suspended in 5% FBS-DMEM, inoculated to dish of a diameter of 3.5 cm (47,200 /dish), and cultured at 37 degrees for seven hours, and thereafter the medium was replaced with a culture medium in which DMSO or test compound of prescribed concentration was added to 0.25% FBS-DMEM containing 4 nM EGF, and it was cultured for seven days. The DNA quantity of cells was determined by fluorescence method, and proliferation acceleration ratio was determined.

(0046)

The results are shown in Figure 1. The EGF dependent proliferation was promoted by 40-50 % by the co-presence retinoic acid of 10 [power -6] M concentration. Using the EGF dependent proliferation by this retinoic acid as index, retinoid action of aforesaid compound was examined. As

a result, 6-(3,4-diethylphenyl carbamoyl) nicotinic acid showed proliferation promotion action by 30 % at 10 [power -5] M and by 20 % at 10 [power -6] M, and 6-(3,4-diethylphenyl carboxamide) nicotinic acid showed proliferation promotion action of 20 % at 10 [power -6] M.

(0047)

Example 2:. Flattening action of hairless mouse skin surface configuration (hide furrow) by topical application.

By topical application or internal administration of retinoic acid, skin assumes a reddish tinge and is changed to a glossy and transparent state. Utilising that similar phenomenon can be reproduced with hairless mouse, the action of topical agent of this invention was compared with retinoic acid using a quantitative index corresponding to the change thereof. Retinoic acid acetone solution of 0.05 %, 0.025 % and 0.01 %, and each 1 % acetone solutions of 6-(3,4-diethylphenyl carbamoyl) nicotinic acid, 6-(3,4-diethylphenyl carboxamide) nicotinic acid, 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid and 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid shown in Production Examples, and acetone were respectively applied onto hairless mouse for 30 days (5 times / weeks), and replica of skin surface was cast using silicon series resin on the following day of the final application day, and the various kinds of parameters showing the characteristics of skin surface configuration were determined using image analysis apparatus.

(0048)

By repeated application of retinoic acid, the skin changed concentration dependently to a skin with a reddish tinge and gloss, and retinoid skin-like change observed in human, was produced. Hide crest disappeared on replica with respect to this change, and it was regarded as the change that surface became flattened. It is known that the image analysis parameter KSD (dispersion of luminance distribution in KSD = 3.9 mm x 3.9 mm) is correlated to hide furrow depth (contemporary dermatology system • yearly edition 90B), and this value corresponded well with the action of retinoic acid (Table 1). In each case, the compounds obtained with Production Examples produced retinoic acid-like changes, and although weaker than retinoic acid, KSD change was observed. In histological examination, the inflammatory changes (cell infiltration within dermis and epidermis, intercellular • intracellular edema, vasodilation and the like) found in retinoic acid were not observed in any of the test compounds. The clearest change was acanthosis (Table 2)

(0049)

(Table 1)

KSD change (%)

| | |
|---|---|
| Acetone | 89.7% |
| 0.01 % retinoic acid | 79.2 % |
| 0.025 % retinoic acid | 73.4 % |
| 0.05 % retinoic acid | 33.6 % |
| 1 % 6-(3,4-diethylphenyl carbamoyl) nicotinic acid | 84.5 % |
| 1 % 6-(3,4-diethylphenyl carboxamide) nicotinic acid | 83.7 % |
| 1 % 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid | 78.3 % |
| 1 % 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid | 76.9 % |

(0050)

(Table 2)

| | Acanthosis (μm) |
|---|---|
| Acetone | 18 μm |
| 0.01 % retinoic acid | 48 μm |
| 1 % 6-(3,4-diethylphenyl carbamoyl) nicotinic acid | 22μm |
| 1 % 6-(3,4-diethylphenyl carboxamide) nicotinic acid | 21 μm |
| 1 % 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid | 32 μm |
| 1 % 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid | 35 μm |

(0051)

Example 3: Action with respect to rhinomouse skin.

On the epidermis of the rhinomouse, egg shaped cysts (utricle) that contain keratin derived from trichocyst are present. This egg shaped cyst is known to shrink due to retinoic acid administration (doe example, Ashton, R. E. et al, J. Invest. Dermatol., 82, pp. 632-635, 1984 and the like). The aforesaid action was examined with respect to the compounds shown in Production Examples. Test compound solution of prescribed concentration and carrier 0.1 ml were applied onto dorsal skin of 8 week old female rhinomouse in a frequency of once or twice per day, 5 days per week over two week period. For the purpose of histological evaluation, the dorsal skin was excised, the epidermis was separated from the dermis using 0.5 % acetic acid, and epidermis sheet for light microscopy observation was produced. The image data obtained via CCD camera was analysed, and the area of egg shaped cysts was determined. The results are shown in Table 3. The retinoic acid showed strong skin flare, but skin flare was not observed at all with the compounds shown in Production Examples.

(0052)

(Table 3)

| | Decrease of egg shaped cysts area (vs carrier, %) | | | | | |
|---|---|---|---|---|---|---|
| | 0.00001 % | 0.0001 % | 0.001% | 0.01 % | 0.1 % | 1 % |
| Retinoic acid | 77 | 59 | 15 | | | |

| | | | |
|---|---|---|---|
| 1% 6-(3,4-diethylphenyl carbamoyl) nicotinic acid | 90 | 87 | 60 |
| 1% 6-(3,4-diethylphenyl carboxamide) nicotinic acid | 95 | 89 | 50 |
| 1% 6-(3,5-di-tert-butylphenyl carbamoyl) nicotinic acid | 80 | 62 | 40 |
| 1% 6-(3,5-di-tert-butylphenyl carboxamide) nicotinic acid | 81 | 58 | 30 |

(0053)

Example 4: Metabolic Test.

One of the reason why the retinoic acid shows toxicity in human, is that the retinoic acid is hard to be metabolised. Therefore, the metabolism of two types of the compounds shown in Production Examples was evaluated by the following method. The test substance which was dissolved in ethanol was added to a buffer containing a specified quantity of rat liver homogenate (25 % homogenate in which rat liver 25 g from which blood was eliminated by irrigation with 0.15 M KCl solution was homogenised with 75 ml phosphate-buffered liquid of pH 7) (final concentration 10 [power -4] M), and the residual quantity of test substance was determined with time by HPLC. The results are shown in Table 4. From the obtained results, it was indicated that the compounds of this invention were readily metabolised in vivo.

(0054)

(Table 4)

Metabolism in rate liver homogenate

| Compound | Residual quantity after 10 min. (%) | Residual quantity after 60 min. (%) |
|---|---|---|
| 6-(3,4-diethylphenyl carbamoyl) nicotinic acid | 65 | 5.0 |
| 6-(3,4-diethylphenyl carboxamide) nicotinic acid | 55 | 3.0 |

*t = 0 as 100 %

(0055)

Example 5: stability test

Ethanol solution of each compound 300 ppm obtained in Production Examples was irradiated with xenon light for 30 hours, or was stored at 50 degrees two months, thereafter the residual quantity was determined by HPLC. As a result, all the compound was confirmed to be remaining by 95 % or more. On the other hand, retinoic acid was rapidly decomposed under the same conditions.

(0056)

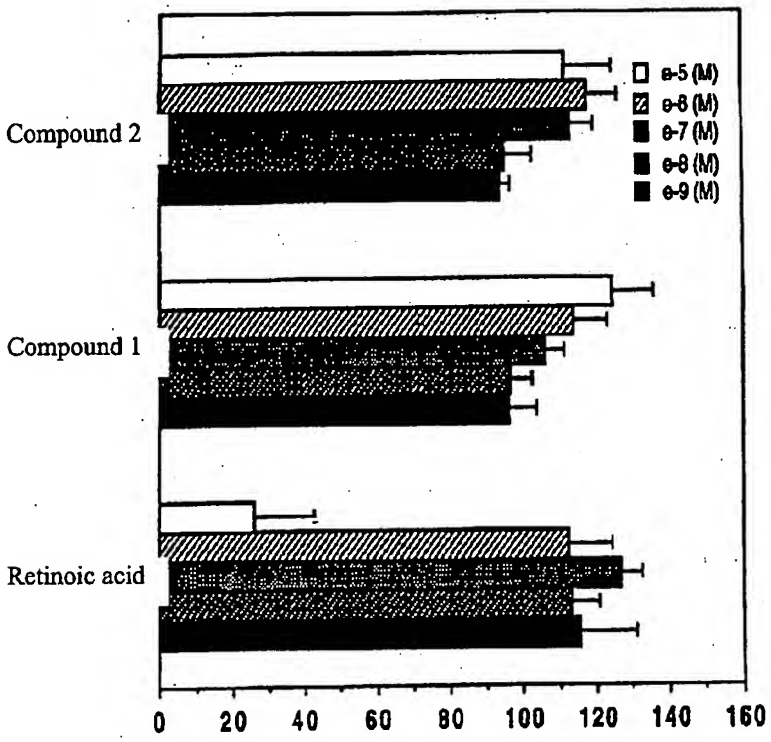
(Advantages Afforded by this Invention)

The compound of aforesaid formula which is a component of topical agent of this invention has excellent skin deterioration prevention action, and, in addition, it is stable, percutaneous absorption is small, and safety is high. Moreover, even when absorbed in body, it is readily metabolised, therefore, there is a characteristic that side effect due to retinoid action is not caused.

(Brief Description of the Figures)

(Figure 1) It is a figure showing the action of representative compounds contained in topical agent of this invention on the EGF dependent proliferation of fibroblast. Compound 1 in figure shows 6-(3,4-diethylphenyl carbamoyl) nicotinic acid, and compound 2 shows 6-(3,4-diethylphenyl carboxamide) nicotinic acid.

(Figure 1)



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